```
=> file hcaplus; d que l14
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FILE COVERS 1907 - 11 Feb 2005  VOL 142 ISS 7
FILE LAST UPDATED: 9 Feb 2005  (20050209/ED)
```

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```
L1             4 SEA FILE=CAPLUS ABB=ON  PLU=ON  MURAMATSU T?/AU AND OKAMOTO
                 K?/AU
L13         3145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (IKEMATSU S? OR ODA M? OR
                 KUMAI H? OR SAKUMA S?)/AU
L14            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L13
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=> file medline; d que l30
FILE 'MEDLINE' ENTERED AT 12:45:12 ON 11 FEB 2005
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FILE LAST UPDATED: 10 FEB 2005 (20050210/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

Warning: The search L-number/HUMAN limit is missing from records indexed with the new 2005 MeSH (records added since December 19, 2004). Until this is corrected, include HUMANS/CT and 20041219-20051231/ED in searches to limit results to humans for this time period.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

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```
L1             4 SEA FILE=CAPLUS ABB=ON  PLU=ON  MURAMATSU T?/AU AND OKAMOTO
                 K?/AU
L13         3145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (IKEMATSU S? OR ODA M? OR
                 KUMAI H? OR SAKUMA S?)/AU
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```
L30             4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L13


=> file embase; d que l43
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L1              4 SEA FILE=CAPLUS ABB=ON  PLU=ON  MURAMATSU T?/AU AND OKAMOTO
                  K?/AU
L13          3145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (IKEMATSU S? OR ODA M? OR
                  KUMAI H? OR SAKUMA S?)/AU
L43             3 SEA FILE=EMBASE ABB=ON  PLU=ON  L1 AND L13


=> file biosis; d que l56
FILE 'BIOSIS' ENTERED AT 12:45:30 ON 11 FEB 2005
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 9 February 2005 (20050209/ED)

FILE RELOADED: 19 October 2003.


L1              4 SEA FILE=CAPLUS ABB=ON  PLU=ON  MURAMATSU T?/AU AND OKAMOTO
                  K?/AU
L13          3145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (IKEMATSU S? OR ODA M? OR
                  KUMAI H? OR SAKUMA S?)/AU
L56             3 SEA FILE=BIOSIS ABB=ON  PLU=ON  L1 AND L13


=> file wpix; d que l71
FILE 'WPIX' ENTERED AT 12:45:39 ON 11 FEB 2005
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FILE LAST UPDATED:          7 FEB 2005      <20050207/UP>
MOST RECENT DERWENT UPDATE:     200509        <200509/DW>
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HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT <<<

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Derwent Chemistry Resource display fields <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
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http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
FOR DETAILS. <<<

```
L1             4 SEA FILE=CAPLUS ABB=ON  PLU=ON  MURAMATSU T?/AU AND OKAMOTO
                 K?/AU
L13         3145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (IKEMATSU S? OR ODA M? OR
                 KUMAI H? OR SAKUMA S?)/AU
L71            1 SEA FILE=WPIX ABB=ON  PLU=ON  L1 AND L13


=> dup rem l30 l14 l43 l56 l71
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PROCESSING COMPLETED FOR L30
PROCESSING COMPLETED FOR L14
PROCESSING COMPLETED FOR L43
PROCESSING COMPLETED FOR L56
PROCESSING COMPLETED FOR L71
L86            4 DUP REM L30 L14 L43 L56 L71 (11 DUPLICATES REMOVED)
                 ANSWERS '1-4' FROM FILE HCAPLUS

=> d ibib ed ab l86 1-4

L86  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2004:512007  HCAPLUS
DOCUMENT NUMBER:          141:134619
TITLE:                    Midkine protects hepatocellular carcinoma cells
                          against TRAIL-mediated apoptosis through
                          down-regulation of caspase-3 activity
AUTHOR(S):                Ohuchida, Tomoko; Okamoto, Kohji; Akahane,
                          Kazuhisa; Higure, Aiichiro; Todoroki, Hidekazu; Abe,
                          Yukio; Kikuchi, Makoto; Ikematsu, Shinya;
```

Muramatsu, Takashi; Itoh, Hideaki
CORPORATE SOURCE: Department of Surgery I, University of Occupational and Environmental Health, Kitakyushu, Japan
SOURCE: Cancer (New York, NY, United States) (2004), 100(11), 2430-2436
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 25 Jun 2004
AB It is believed that midkine (MK), a heparin-binding growth factor, plays an important role in carcinogenesis. However, the biol. mechanism of MK in hepatocellular carcinoma was not clarified to date. The objective of the current study was to investigate the antiapoptotic role of MK in a human hepatoma cell line. The human hepatoma cell line HepG2 was used to study the antiapoptotic effect of MK. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)/actinomycin D (ActD)-induced apoptosis was detected using a 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium monosodium salt (WST-8) assay, a caspase-3 activity assay, a caspase-8 activity assay, and flow cytometric anal. TRAIL had a potent, dose-dependent inductive effect on cell death in HepG2 cells, for which viable cell counts decreased to 6.3% of the control count at a TRAIL concentration of 100 ng/mL in the presence of 500 ng/mL ActD. Flow cytometry was used to demonstrate that apoptosis induced by TRAIL/ActD was in fact the cause of cell death. According to the WST-8 assay, MK pretreatment resulted in the suppression of TRAIL/ActD-mediated apoptosis in HepG2 cells, although cell viability did not increase when HepG2 cells were treated with MK alone. Caspase-3 activity was down-regulated when MK was added, but caspase-8 activity was high in both the absence and presence of MK. The results of the current study indicate that MK acts as an antiapoptotic factor in HepG2 cells through the down-regulation of caspase-3 activity.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:448733 HCAPLUS
DOCUMENT NUMBER: 139:131632
TITLE: High levels of urinary midkine in various cancer patients
AUTHOR(S): **Ikematsu, Shinya**; **Okamoto, Kohji**; Yoshida, Yoshihiro; **Oda, Munehiro**; Sugano-Nagano, Hitomi; Ashida, Kinya; **Kumai, Hideshi**; Kadomatsu, Kenji; Muramatsu, Hisako; **Muramatsu, Takashi**; **Sakuma, Sadatoshi**
CORPORATE SOURCE: Meiji Dairies Corporation, Odawara, Kanagawa, 250-0862, Japan
SOURCE: Biochemical and Biophysical Research Communications (2003), 306(2), 329-332
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 Jun 2003
AB Midkine (MK) is a heparin-binding growth factor, which promotes growth, migration, and survival of various cells, and MK expression is increased in many human carcinomas. We determined the urinary MK level by enzyme-linked immunoassay. Taking 311 pg/mg creatinine as a cut-off level, 70% of patients with various carcinomas (n=142) gave pos. values, while only 5.5%

of healthy volunteers (n=330) did. In case of gastric carcinoma, 17 out of 21 patients with stage 1 tumor were pos. Urinary MK levels are expected to become a convenient marker as an aid in detection of tumors.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2001:208510 HCAPLUS
DOCUMENT NUMBER: 134:204750
TITLE: Early cancer diagnosis using midkine as tumor marker
INVENTOR(S): **Muramatsu, Takashi; Okamoto, Kohji ; Ikematsu, Shinya; Oda, Munehiro; Kumai, Hideshi; Sakuma, Sadatoshi**
PATENT ASSIGNEE(S): Meiji Milk Products Co., Ltd, Japan
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001020333	A1	20010322	WO 2000-JP6147	20000908
W: AU, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2384579	AA	20010322	CA 2000-2384579	20000908
AU 2000068760	A5	20010417	AU 2000-68760	20000908
EP 1215500	A1	20020619	EP 2000-957049	20000908
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				

PRIORITY APPLN. INFO.:

JP 1999-256678	A	19990910
JP 1999-345404	A	19991203
JP 2000-33168	A	20000210
WO 2000-JP6147	W	20000908

ED Entered STN: 22 Mar 2001
AB It is found out that MK (midkine) appears in the blood or urine of patients with various cancers (e.g., stomach cancer, hepatocellular carcinoma, lung cancer) in their early stages. Based on this finding, a method is completed for diagnosing an early cancer by immunol. measuring MK and/or its fragment in the blood or urine sample.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2000:717208 HCAPLUS
DOCUMENT NUMBER: 134:161004
TITLE: Serum midkine levels are increased in patients with various types of carcinomas
AUTHOR(S): **Ikematsu, S.**; Yano, A.; Aridome, K.; Kikuchi, M.; **Kumai, H.**; Nagano, H.; **Okamoto, K.**; **Oda, M.**; **Sakuma, S.**; Aikou, T.; Muramatsu, H.; Kadomatsu, K.; **Muramatsu, T.**
CORPORATE SOURCE: Meiji Cell Technology Center, Odawara, 250-0862, Japan
SOURCE: British Journal of Cancer (2000), 83(6), 701-706
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.

already have

DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 11 Oct 2000
AB The level of expression of midkine (MK), a heparin-binding growth factor, is increased in many types of human carcinomas. An enzyme-linked immunoassay, which utilizes a combination of rabbit and chicken antibodies revealed that serum MK level in the controls (n = 135) was 0.154 ± 0.076 (mean ± SD) ng ml-1 with an apparent cut-off value as 0.5 ng ml-1. Serum MK level was significantly elevated in the cancer patients (n = 150) ($P < 0.001$); 87% of the patients showed levels of more than 0.5 ng ml-1. All ten types of cancer examined showed a similar profile of serum MK level. There was no or weak correlation between C-reactive protein level, a marker of inflammation, and serum MK level. Furthermore, in case of gastric carcinoma and lung carcinoma, patients with stage I carcinoma already showed elevated serum MK levels. The present results indicated that serum MK could serve as a general tumor marker with a good potential for clin. application.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> file hcaplus; d que l9; d que l12; d que l27; d que l29
FILE 'HCAPLUS' ENTERED AT 12:48:21 ON 11 FEB 2005
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FILE COVERS 1907 - 11 Feb 2005  VOL 142 ISS 7
FILE LAST UPDATED: 9 Feb 2005  (20050209/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L3          386 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MIDKINES+OLD,PFT/CT
L4        10797 SEA FILE=HCAPLUS ABB=ON  PLU=ON  TUMOR MARKERS+PFT/CT
L5        38794 SEA FILE=HCAPLUS ABB=ON  PLU=ON  URINE ANALYSIS/CT
L6        93484 SEA FILE=HCAPLUS ABB=ON  PLU=ON  URINE/CT
L9            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND L4 AND (L5 OR L6)


L3          386 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MIDKINES+OLD,PFT/CT
L4        10797 SEA FILE=HCAPLUS ABB=ON  PLU=ON  TUMOR MARKERS+PFT/CT
L7       378527 SEA FILE=HCAPLUS ABB=ON  PLU=ON  BLOOD SERUM+ALL/CT
L12           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND L4 AND L7


L1            4 SEA FILE=CAPLUS ABB=ON  PLU=ON  MURAMATSU T?/AU AND OKAMOTO
                K?/AU
L3          386 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MIDKINES+OLD,PFT/CT
L13        3145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (IKEMATSU S? OR ODA M? OR
                KUMAI H? OR SAKUMA S?)/AU
L14           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L13
L16      704622 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?NEOPLAS? OR ?CARCINOM? OR
                ?TUMOR? OR ?METASTA? OR ?TUMOR? OR ?TUMOUR?
L18     1543088 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HUMAN
L20          22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) DGN/RL
L21          12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) ANT/RL
L22          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) ANST/RL
L23          60 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) THU/RL
L25          39 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L20 OR L21 OR L22 OR L23)
                AND L16 AND L18
L26          36 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 NOT L14
L27          23 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 NOT (PROSTATE OR GD2 OR
                INDUCTION OR HYDROXIDE OR RADIOSENS? OR HARP OR OINTMENTS OR
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ENDOHEL? OR ARPE OR MICROARRA? OR TRUNCATED)/TI

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L1            4 SEA FILE=CAPLUS ABB=ON  PLU=ON  MURAMATSU T?/AU AND OKAMOTO
                K?/AU
L3          386 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MIDKINES+OLD,PFT/CT
L13        3145 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (IKEMATSU S? OR ODA M? OR
                KUMAI H? OR SAKUMA S?)/AU
L14           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L13
L16      704622 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?NEOPLAS? OR ?CARCINOM? OR
                ?TUMOR? OR ?METASTA? OR ?TUMOR? OR ?TUMOUR?
L18     1543088 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HUMAN
L20          22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) DGN/RL
L21          12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) ANT/RL
L22          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) ANST/RL
L23          60 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 (L) THU/RL
L25          39 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L20 OR L21 OR L22 OR L23)
                AND L16 AND L18
L26          36 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 NOT L14
L29           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND (TRUNCATED MIDKINE)/TI


=> s (l9 or l12 or l27 or l29) not l14      L14 = inventors
L87          25 (L9 OR L12 OR L27 OR L29) NOT L14

=> file medline; d que l38; d que l42
FILE 'MEDLINE' ENTERED AT 12:49:09 ON 11 FEB 2005

 FILE LAST UPDATED: 10 FEB 2005 (20050210/UP). FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 Warning: The search L-number/HUMAN limit is missing from records indexed
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 this is corrected, include HUMANS/CT and 20041219-20051231/ED in
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 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
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L32          308 SEA FILE=MEDLINE ABB=ON  PLU=ON  MIDKINE
L34        85741 SEA FILE=MEDLINE ABB=ON  PLU=ON  TUMOR MARKERS, BIOLOGICAL+NT/C
                T
L38           12 SEA FILE=MEDLINE ABB=ON  PLU=ON  L32 AND L34


L32          308 SEA FILE=MEDLINE ABB=ON  PLU=ON  MIDKINE
L33      1565183 SEA FILE=MEDLINE ABB=ON  PLU=ON  NEOPLASMS+NT/CT
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L41      238265 SEA FILE=MEDLINE ABB=ON  PLU=ON  L33 (L) DI/CT
L42           5 SEA FILE=MEDLINE ABB=ON  PLU=ON  L32 AND L41


=> s (l38 or l42) not l30   L30 = inventors
           912 MURAMATSU T?/AU
          1836 OKAMOTO K?/AU
            62 IKEMATSU S?/AU
           904 ODA M?/AU
            14 KUMAI H?/AU
           520 SAKUMA S?/AU
L88         12 (L38 OR L42) NOT L30

=> file embase; d que l50; d que l51; d que l53; d que l54
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L44          221 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L45        14779 SEA FILE=EMBASE ABB=ON  PLU=ON  TUMOR MARKER/CT
L50            8 SEA FILE=EMBASE ABB=ON  PLU=ON  L44 AND L45



L44          221 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L46        30441 SEA FILE=EMBASE ABB=ON  PLU=ON  CANCER DIAGNOSIS/CT
L51            1 SEA FILE=EMBASE ABB=ON  PLU=ON  L44 AND L46



L44          221 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L47      1259601 SEA FILE=EMBASE ABB=ON  PLU=ON  NEOPLASM+NT/CT
L48        53496 SEA FILE=EMBASE ABB=ON  PLU=ON  SERUM/CT
L53            0 SEA FILE=EMBASE ABB=ON  PLU=ON  L44 AND L47 AND L48



L44          221 SEA FILE=EMBASE ABB=ON  PLU=ON  MIDKINE/CT
L47      1259601 SEA FILE=EMBASE ABB=ON  PLU=ON  NEOPLASM+NT/CT
L49       275847 SEA FILE=EMBASE ABB=ON  PLU=ON  URIN?
L54            1 SEA FILE=EMBASE ABB=ON  PLU=ON  L44 AND L47 AND L49


=> s (l50 or l51 or l54) not l43   L43 = inventors
L89            8 (L50 OR L51 OR L54) NOT L43

=> file biosis; d que l64; d que l67; d que l70
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FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 9 February 2005 (20050209/ED)

FILE RELOADED: 19 October 2003.

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L57         371 SEA FILE=BIOSIS ABB=ON  PLU=ON  MIDKINE
L58           1 SEA FILE=BIOSIS ABB=ON  PLU=ON  CYTOKINE MK
L59       14587 SEA FILE=BIOSIS ABB=ON  PLU=ON  (TUMOR OR TUMOUR) (W) MARKER
L64           6 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L57 OR L58) AND L59


L57         371 SEA FILE=BIOSIS ABB=ON  PLU=ON  MIDKINE
L58           1 SEA FILE=BIOSIS ABB=ON  PLU=ON  CYTOKINE MK
L60     1504810 SEA FILE=BIOSIS ABB=ON  PLU=ON  ?CANCER? OR ?TUMOR? OR
                ?TUMOUR? OR ?NEOPLAS? OR ?CARCINO? OR ?METASTA?
L62      596215 SEA FILE=BIOSIS ABB=ON  PLU=ON  SERUM
L66          12 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L57 OR L58) AND L60 AND L62
L67           3 SEA FILE=BIOSIS ABB=ON  PLU=ON  L66 AND (IMMUNOASSAY OR
                BLOOD)/TI


L57         371 SEA FILE=BIOSIS ABB=ON  PLU=ON  MIDKINE
L58           1 SEA FILE=BIOSIS ABB=ON  PLU=ON  CYTOKINE MK
L63      525396 SEA FILE=BIOSIS ABB=ON  PLU=ON  URIN?
L70           1 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L57 OR L58) AND L63 AND HUMAN
                AND URINARY/TI

=> s (l64 or l67 or l70) not l56    L56 = inventors
L90           7 (L64 OR L67 OR L70) NOT L56

=> file wpix; d que l77; d que l80; d que l83; d que l85
FILE 'WPIX' ENTERED AT 12:51:19 ON 11 FEB 2005
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MOST RECENT DERWENT UPDATE:     200509        <200509/DW>
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    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

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    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<
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L72          77 SEA FILE=WPIX ABB=ON  PLU=ON  MIDKINE OR CYTOKINE MK
L73         424 SEA FILE=WPIX ABB=ON  PLU=ON  (TUMOR OR TUMOUR) (W) MARKER
L77           0 SEA FILE=WPIX ABB=ON  PLU=ON  L72 AND L73



L72          77 SEA FILE=WPIX ABB=ON  PLU=ON  MIDKINE OR CYTOKINE MK
L74      107570 SEA FILE=WPIX ABB=ON  PLU=ON  ?NEOPLAS? OR ?TUMOR? OR ?TUMOUR?
                OR ?CANCER? OR ?METASTA? OR ?CARCINO? OR ?CANCER?
L79           6 SEA FILE=WPIX ABB=ON  PLU=ON  L72 AND L74 AND ?DIAG?
L80           3 SEA FILE=WPIX ABB=ON  PLU=ON  L79 NOT (CARBOXY? OR ADIPOSE OR
                MRNA)/TI



L72          77 SEA FILE=WPIX ABB=ON  PLU=ON  MIDKINE OR CYTOKINE MK
L74      107570 SEA FILE=WPIX ABB=ON  PLU=ON  ?NEOPLAS? OR ?TUMOR? OR ?TUMOUR?
                OR ?CANCER? OR ?METASTA? OR ?CARCINO? OR ?CANCER?
L76       26813 SEA FILE=WPIX ABB=ON  PLU=ON  URIN?
L83           1 SEA FILE=WPIX ABB=ON  PLU=ON  L72 AND L74 AND L76



L72          77 SEA FILE=WPIX ABB=ON  PLU=ON  MIDKINE OR CYTOKINE MK
L74      107570 SEA FILE=WPIX ABB=ON  PLU=ON  ?NEOPLAS? OR ?TUMOR? OR ?TUMOUR?
                OR ?CANCER? OR ?METASTA? OR ?CARCINO? OR ?CANCER?
L84          17 SEA FILE=WPIX ABB=ON  PLU=ON  L72 AND L74 AND HUMAN
L85           1 SEA FILE=WPIX ABB=ON  PLU=ON  L84 AND SCREENING/TI


=> s (l80 or l83 or l85) not l71
L91           4 (L80 OR L83 OR L85) NOT L71

=> dup rem l88 l87 l89 l90 l91
FILE 'MEDLINE' ENTERED AT 12:52:02 ON 11 FEB 2005

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PROCESSING COMPLETED FOR L87
PROCESSING COMPLETED FOR L89
PROCESSING COMPLETED FOR L90
PROCESSING COMPLETED FOR L91
L92           40 DUP REM L88 L87 L89 L90 L91 (16 DUPLICATES REMOVED)
                 ANSWERS '1-12' FROM FILE MEDLINE
                 ANSWERS '13-32' FROM FILE HCAPLUS
                 ANSWERS '33-35' FROM FILE EMBASE
                 ANSWERS '36-37' FROM FILE BIOSIS
                 ANSWERS '38-40' FROM FILE WPIX

=> d ibib ed ab l92 1-37; d ibib ab abex l92 38-40

L92  ANSWER 1 OF 40     MEDLINE on STN                    DUPLICATE 4
ACCESSION NUMBER:    2003270879     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 12771916
TITLE:               Correlation of elevated level of blood midkine
                     with poor prognostic factors of human neuroblastomas.
AUTHOR:              Ikematsu S; Nakagawara A; Nakamura Y; Sakuma S; Wakai K;
                     Muramatsu T; Kadomatsu K
CORPORATE SOURCE:    Department of Biochemistry, Nagoya University Graduate
                     School of Medicine, 65 Tsurumai-cho, Showaku, Nagoya
                     466-8550, Japan.
SOURCE:              British journal of cancer, (2003 May 19) 88 (10) 1522-6.
                     Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY:        England: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200306
ENTRY DATE:          Entered STN: 20030612
                     Last Updated on STN: 20030627
                     Entered Medline: 20030626
ED   Entered STN: 20030612
     Last Updated on STN: 20030627
     Entered Medline: 20030626
AB   The heparin-binding growth factor midkine (MK) is the product of
     a retinoic acid-responsive gene, and is implicated in neuronal survival
     and differentiation, and carcinogenesis. We previously reported that MK
     mRNA expression is elevated in neuroblastoma specimens at all stages,
     whereas pleiotrophin, the other member of the MK family, is expressed at
     high levels in favourable neuroblastomas. As MK is a secretory protein,
     it can be detected in the blood. Here, we show a significant correlation
     of the plasma MK level with prognostic factors of neuroblastomas. The
     plasma MK level was determined in 220 patients with neuroblastomas, and
     compared with that in children without malignant tumors (n=17, <500 pg
     ml(-1)). The plasma MK level became significantly elevated with advancing
     stages (stage 1: 445 pg ml(-1) (median), n=73; stage 2: 589, n=39; stage
     3: 864, n=40; stage 4: 1445, n=56; and stage 4S: 2439, n=12). More
     importantly, a higher MK level was strongly correlated with poor
     prognostic factors: over 1 year of age (P=0.0299), MYCN amplification
     (P<0.0001), low TrkA expression (P=0.0005), nonmass screening, sporadic
     neuroblastomas (P<0.0001), and diploidy/tetraploidy (P=0.0007). Thus,
     these results demonstrate that the plasma MK level is a good marker for
     evaluating the progression of neuroblastomas. Moreover, considering the
     ability of antisense MK oligodeoxyribonucleotide to suppress tumour growth
```

of colorectal carcinoma cells in nude mice, as recently reported, the present study suggests that MK is a possible candidate molecular target for therapy for neuroblastomas.

L92 ANSWER 2 OF 40 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003314002 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12841873
TITLE: Preoperative serum **midkine** concentration is a prognostic marker for esophageal squamous cell carcinoma.
AUTHOR: Shimada Hideaki; Nabeya Yoshihiro; Tagawa Masatoshi; Okazumi Shin-ichi; Matsubara Hisahiro; Kadomatsu Kenji; Muramatsu Takashi; Ikematsu Shinya; Sakuma Sadatoshi; Ochiai Takenori
CORPORATE SOURCE: Department of Academic Surgery, Graduate School of Medicine, Chiba University, Chuo-ku, Chiba 260-8677, Japan.. hshimada@med.m.chiba-u.ac.jp
SOURCE: Cancer science, (2003 Jul) 94 (7) 628-32. Journal code: 101168776. ISSN: 1347-9032.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20030708
Last Updated on STN: 20040107
Entered Medline: 20040106

ED Entered STN: 20030708
Last Updated on STN: 20040107
Entered Medline: 20040106

AB High preoperative serum **midkine** concentration is associated with poor survival in patients with esophageal cancer, even after radical surgery, and thus may have prognostic value. **Midkine** (MK), a heparin-binding growth factor, is expressed in numerous cancer tissues, and serum MK (S-MK) concentrations are increased in patients with various neoplasms. The aim of this study is to evaluate the clinical significance of S-MK in patients with esophageal squamous cell cancer (SCC). S-MK was measured by enzyme-linked immunosorbent assay in 135 healthy controls, 16 patients with benign esophageal disease, and 93 patients with primary esophageal SCC before surgery. The serum concentrations of carcinoembryonic antigen (CEA), SCC antigen (SCC-Ag), and cytokeratin 19 fragment (CYFRA21-1) were also evaluated. All patients with esophageal SCC underwent radical esophagectomy. Tumor MK expression was assessed by immunohistochemistry in 14 fresh tumor specimens. To determine whether S-MK is of value as a prognostic factor, the authors conducted a survival analysis using Cox's proportional hazards model. S-MK values in patients with esophageal SCC were significantly higher than those in healthy controls (417 +/- 342 pg/ml vs. 154 +/- 76 pg/ml, $P < 0.001$). Using 300 pg/ml as the cut-off value (representing the mean + 2 standard deviations of the S-MK of healthy controls), 61% of patients with esophageal SCC were classified as positive. MK expression by the tumor was significantly associated with high level of S-MK. High S-MK (>/= 300 pg/ml) was associated with tumor size, immunoreactivity and poor survival. Multivariate analysis indicated that S-MK was an independent prognostic factor. S-MK may be a useful tumor marker for esophageal SCC. Increased preoperative S-MK in patients with esophageal SCC is associated with poor survival.

L92 ANSWER 3 OF 40 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2003069042 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12579281
TITLE: Increased serum **midkine** concentration as a possible tumor marker in patients with superficial esophageal cancer.
AUTHOR: Shimada Hideaki; Nabeya Yoshihiro; Okazumi Shin-ichi; Matsubara Hisahiro; Kadomatsu Kenji; Muramatsu Takashi; Ikematsu Shinya; Sakuma Sadatoshi; Ochiai Takenori
CORPORATE SOURCE: Department of Academic Surgery, Graduate School of Medicine, Chiba University, Chiba 260-8677, Japan.. hshimada@med.m.chiba-u.ac.jp
SOURCE: Oncology reports, (2003 Mar-Apr) 10 (2) 411-4. Journal code: 9422756. ISSN: 1021-335X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030212
Last Updated on STN: 20030730
Entered Medline: 20030729
ED Entered STN: 20030212
Last Updated on STN: 20030730
Entered Medline: 20030729
AB **Midkine**, a heparin-binding growth factor, is expressed in numerous cancer tissues and is reportedly elevated in patients with various neoplasms. The aim of this study was to evaluate the clinicopathological significance of serum **midkine** concentration (S-MK) in patients with superficial esophageal squamous cell carcinoma (SCC). Pretreatment S-MK was measured by enzyme-linked immunosorbent assay in 135 healthy controls, 16 patients with benign esophageal disease, and 60 patients with primary superficial esophageal squamous cell cancer (SESCC). All patients with SESCC underwent curative resection. The disease was staged according to TNM/UICC guidelines. Serum concentrations of carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), and cytokeratin 19 fragment (CYFRA21-1) were also evaluated in the same populations. S-MK in patients with SESCC (388+/-411 pg/ml) was significantly higher than in benign esophageal disease or healthy controls (183+/-73 and 154+/-76 pg/ml, respectively). Using the mean + 2 standard deviations of healthy control S-MK (300 pg/ml) as the cut-off level, 50% of patients with esophageal SESCC were deemed positive. This S-MK positivity rate for detecting SESCC was significantly higher than for other tumor markers. Thus, S-MK may be useful as a tumor marker to detect SESCC.

L92 ANSWER 4 OF 40 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2000091629 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10626184
TITLE: Expression of the **midkine** gene in human hepatocellular carcinomas.
AUTHOR: Koide N; Hada H; Shinji T; Ujike K; Hirasaki S; Yumoto Y; Hanafusa T; Kadomatsu K; Muramatsu H; Muramatsu T; Tsuji T
CORPORATE SOURCE: First Department of Internal Medicine, Okayama University School of Medicine, Japan.. koide@hospital.okayama-u.ac.jp
SOURCE: Hepato-gastroenterology, (1999 Nov-Dec) 46 (30) 3189-96. Journal code: 8007849. ISSN: 0172-6390.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127
ED Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127
AB BACKGROUND/AIMS: Aberrant expression of **Midkine** (MK) has been found in various human carcinomas including hepatocellular carcinoma (HCC). The aim of study is to identify the incidence of MK expression in tumor and surrounding non-tumor tissues of the liver, and to find the correlation of MK expression with other tumor markers. METHODOLOGY: Liver tissues were obtained from 16 patients with HCC and 4 with metastatic liver cancer. Background diseases of the HCC patients include liver cirrhosis and chronic hepatitis of type B or C. RNA was prepared from both cancerous and surrounding non-cancerous tissues, and analyzed for the presence of MK mRNA by RT-PCR, PCR-Southern blot, and Northern blot analysis. RESULTS: MK expression was detected in 12 (75%) of 16 HCCs by PCR-Southern blot analysis, the most sensitive of the 3 methods. Three of 9 surrounding cirrhotic tissues were weakly positive for MK expression, and none of chronic hepatitis and 4 normal tissues were negative. No significant difference was found in clinical and pathological parameters between MK negative and positive cases. Among metastatic cancers, 1 of gastric origin was positive for MK expression, but 1 each of chorangiocellular, gall bladder, and gastrinoma origin was negative. CONCLUSIONS: These results suggest that MK is expressed in the majority of HCC tissues and rarely in surrounding tissues in chronic liver diseases.

L92 ANSWER 5 OF 40 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 1998379886 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9716029
TITLE: Truncated **midkine** as a marker of diagnosis and detection of nodal metastases in gastrointestinal carcinomas.
AUTHOR: Aridome K; Takao S; Kaname T; Kadomatsu K; Natsugoe S; Kijima F; Aikou T; Muramatsu T
CORPORATE SOURCE: First Department of Surgery, Kagoshima University Faculty of Medicine, Japan.
SOURCE: British journal of cancer, (1998 Aug) 78 (4) 472-7.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980904
ED Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980904
AB **Midkine** (MK) is a growth factor identified as a product of a retinoic acid-responsive gene. A truncated form of MK mRNA, which lacks a sequence encoding the N-terminally located domain, was recently found in cancer cells. We investigated the expression of the truncated MK mRNA in specimens of 47 surgically removed human gastrointestinal organs using polymerase chain reaction. Truncated MK was not detected in all of the 46 corresponding non-cancerous regions. On the other hand, this short MK mRNA was expressed in the primary tumours in 12 of 16 gastric cancers, 8

of 13 colorectal carcinomas, five of nine hepatocellular carcinomas, two of two oesophageal carcinomas and one ampullary duodenal cancer. In addition, truncated MK was detectable in all of the 14 lymph node metastases but in none of three metastatic sites in the liver, suggesting that truncated MK mRNA could become a good marker of nodal metastases in gastrointestinal tract.

L92 ANSWER 6 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003389627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12926063
TITLE: Regulatory regions of growth-related genes can activate an exogenous gene of the alpha-fetoprotein promoter to a comparable degree in human hepatocellular carcinoma cells.
AUTHOR: Tomizawa Minoru; Saisho Hiromitsu; Tagawa Masatoshi
CORPORATE SOURCE: Division of Pathology, Chiba Cancer Center Research Institute, Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, Chuo-ku, Chiba, Japan.. nihminorcib@umin.ac.jp
SOURCE: Anticancer research, (2003 Jul-Aug) 23 (4) 3273-7. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030821
Last Updated on STN: 20031001
Entered Medline: 20030930
ED Entered STN: 20030821
Last Updated on STN: 20031001
Entered Medline: 20030930
AB We examined the transcriptional activation by the regulatory regions of the **midkine** (MK), survivin (SUR), cyclooxygenase-2 (COX-2), telomerase reverse transcriptase (TERT) and alpha-fetoprotein (AFP) genes in human hepatocellular carcinoma cells. Luciferase assays showed that the SUR regulatory region exhibited the greatest activity and that the MK regulatory region activated the reporter gene better than the enhancer-linked AFP promoter even in high-AFP-producing cells. The COX-2 and TERT regulatory regions also activated the reporter gene better than the AFP enhancer/promoter in intermediate-AFP-producing cells. Combination of the regulatory regions arranged in tandem modulated their transcriptional activities, depending on the arrangement of the promoters and cells examined. These data suggested that the regulatory regions of the growth-related genes could be useful to activate a therapeutic gene in hepatocellular carcinoma cells irrespective of the amounts of AFP production but combinatory use of the promoter regions could not always contribute to enhanced activity.

L92 ANSWER 7 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003424709 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12966430
TITLE: A promoter region of the **midkine** gene that is frequently expressed in human hepatocellular carcinoma can activate a suicide gene as effectively as the alpha-fetoprotein promoter.
AUTHOR: Tomizawa M; Yu L; Wada A; Tamaoki T; Kadomatsu K; Muramatsu T; Matsubara S; Watanabe K; Ebara M; Saisho H; Sakiyama S; Tagawa M
CORPORATE SOURCE: Division of Pathology, Chiba Cancer Center, 666-2, Nitona,

Chuo-ku, Chiba 260-8717, Japan.
SOURCE: British journal of cancer, (2003 Sep 15) 89 (6) 1086-90.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030911
Last Updated on STN: 20031018
Entered Medline: 20031017
ED Entered STN: 20030911
Last Updated on STN: 20031018
Entered Medline: 20031017
AB We examined the expression of the **midkine** (MK) and alpha-fetoprotein (AFP) genes in 15 paired human specimens obtained from hepatocellular carcinoma (HCC) and the corresponding noncancerous regions of the same patients. A total of 14 HCC but none of the noncancerous specimens were positive for the MK mRNA. In contrast, three HCC specimens and one corresponding noncancerous sample out of the three AFP-positive HCC cases expressed the AFP gene. A 2.3-kb genomic fragment in the regulatory region of the MK gene could activate a fused reporter gene in both AFP-producing and -nonproducing HCC lines, and the MK fragment-mediated transcriptional activity was comparable to the AFP enhancer-linked AFP promoter in AFP-producing cell lines. The AFP-producing but not AFP-nonproducing HCC cell lines that were transfected with the MK promoter-linked herpes simplex virus-thymidine kinase (HSV-TK) gene became susceptible to a prodrug ganciclovir to a similar degree of the HCC transfected with the enhancer-linked AFP promoter-fused HSV-TK gene. These data suggest that the MK promoter can activate a therapeutic gene preferentially in HCC and is as useful as the AFP promoter in clinical settings.

L92 ANSWER 8 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003277137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12804566
TITLE: High levels of urinary **midkine** in various cancer patients.
AUTHOR: Ikematsu Shinya; Okamoto Kohji; Yoshida Yoshihiro; Oda Munehiro; Sugano-Nagano Hitomi; Ashida Kinya; Kumai Hideshi; Kadomatsu Kenji; Muramatsu Hisako; Takashi Muramatsu; Sakuma Sadatoshi
CORPORATE SOURCE: Meiji Dairies Corporation, 540 Naruda, Odawara, Kanagawa 250-0862, Japan.
SOURCE: Biochemical and biophysical research communications, (2003 Jun 27) 306 (2) 329-32.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030614
Last Updated on STN: 20030726
Entered Medline: 20030725
ED Entered STN: 20030614
Last Updated on STN: 20030726
Entered Medline: 20030725
AB **Midkine** (MK) is a heparin-binding growth factor, which promotes

growth, migration, and survival of various cells, and MK expression is increased in many human carcinomas. We determined the urinary MK level by enzyme-linked immunoassay. Taking 311pg/mg creatinine as a cut-off level, 70% of patients with various carcinomas (n=142) gave positive values, while only 5.5% of healthy volunteers (n=330) did. In case of gastric carcinoma, 17 out of 21 patients with stage 1 tumor were positive. Urinary MK levels are expected to become a convenient marker as an aid in detection of tumors.

L92 ANSWER 9 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2002427559 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12184064
TITLE: Function and medical significance of a growth factor, **midkine**.
AUTHOR: Muramastu Takashitmurama@med.nagoya-u.ac.jp
SOURCE: Tanpakushitsu kakusan koso. Protein, nucleic acid, enzyme, (2002 Aug) 47 (10) 1259-67. Ref: 67
Journal code: 0413762. ISSN: 0039-9450.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020820
Last Updated on STN: 20021002
Entered Medline: 20021001
ED Entered STN: 20020820
Last Updated on STN: 20021002
Entered Medline: 20021001

L92 ANSWER 10 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2000438675 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10879061
TITLE: Recent progress of **midkine** research on cancer.
AUTHOR: Kadomatsu K
CORPORATE SOURCE: Department of Biochemistry, Nagoya University School of Medicine.
SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2000 Jun) 58 (6) 1337-47. Ref: 27
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000919
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000919
AB **Midkine** is a heparin-binding growth factor, implicated in various biological phenomena such as neuronal survival and differentiation, tissue remodeling and carcinogenesis. Together with pleiotrophin, **midkine** constitutes a family that is distinct from

other heparin-binding growth factors. In this review, I will briefly describe biochemical and biological characteristics of **midkine** and then focus on its biological significance in cancer. The most intriguing feature of **midkine** in cancer is its augmented expression in advanced tumors at very high frequency in non-tissue specific manner. In addition, its high expression is also detected in precancerous lesions. **Midkine** exerts carcinogenesis-related activities, including transforming, anti-apoptotic, angiogenic and fibrinolytic ones. These data provide a possibility of clinical application of **midkine**. Serum **midkine** level can be a useful tumor marker. Gene therapy using its promoter region and therapeutic strategy choosing **midkine** as a molecular target are worth challenging.

L92 ANSWER 11 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2000214462 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10752788
TITLE: A malignant rhabdoid tumor of the kidney occurring concurrently with a brain tumor: report of a case.
AUTHOR: Adachi Y; Takamatsu H; Noguchi H; Tahara H; Fukushige T; Takasaki T; Yoshida A; Kamenosono A; Kikuchi J; Asatani M; Kawakami K
CORPORATE SOURCE: Department of Pediatric Surgery, Faculty of Medicine, Kagoshima University, Japan.
SOURCE: Surgery today, (2000) 30 (3) 298-301.
Journal code: 9204360. ISSN: 0941-1291.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000426
ED Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000426
AB Malignant rhabdoid tumor of the kidney (MRTK) is one of the most lethal neoplasms to occur in young infants. Cases of MRTK accompanying an embryonal tumor in the central nervous system have occasionally been described. We present herein an interesting case of MRTK that was clinically diagnosed preoperatively. A male infant aged 6 months with both a midline brain tumor and a renal neoplasm was transferred to our institution. Although roentgenographic evaluation suggested that the renal lesion was a Wilms' tumor, **midkine** (MK), a growth and differentiation factor characteristically present in the urine of patients with Wilms' tumor, was not detected. A preoperative diagnosis of MRTK was established based on the lack of urinary MK in addition to the typical clinical features of the young age and the concurrent brain tumor.

L92 ANSWER 12 OF 40 MEDLINE on STN
ACCESSION NUMBER: 1999260274 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10331431
TITLE: Monoclonal antibody to human **midkine** reveals increased **midkine** expression in human brain tumors.
AUTHOR: Kato S; Ishihara K; Shinozawa T; Yamaguchi H; Asano Y; Saito M; Kato M; Terada T; Awaya A; Hirano A; Dickson D W;

Yen S H; Ohama E
CORPORATE SOURCE: Division of Neuropathology, Faculty of Medicine, Tottori University, Yonago, Japan.
SOURCE: Journal of neuropathology and experimental neurology, (1999 May) 58 (5) 430-41.
Journal code: 2985192R. ISSN: 0022-3069.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990527
ED Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990527
AB We produced a rat IgG2a monoclonal antibody against the carboxyl terminal region of human **midkine** (MK), a novel growth factor. This monoclonal antibody was used in immunohistochemical studies to compare the expression of MK, proliferating cell nuclear antigen (PCNA) and p53 protein in 133 primary brain tumors and 21 carcinoma metastases to the central nervous system. Approximately half of the glioblastomas multiforme (GBMs) (19/32), medulloblastomas (8/14), primitive neuroectodermal tumors (PNETs) (5/11), breast carcinoma metastases (Br-Mts) (6/10) and lung carcinoma metastases (L-Mts) (5/11) as well as some astrocytomas (2/14) had tumor cells that expressed MK; however, oligodendrogliomas, ependymomas, schwannomas, meningiomas, and pituitary adenomas did not express MK. The values of the PCNA-labeling index were statistically higher in GBMs, medulloblastomas, PNETs, Br-Mts, and L-Mts that expressed MK than in those that did not (Wilcoxon rank-sum test, $p < 0.05$). There was no correlation between MK and p53 protein in all tumor types. Normal and non-neoplastic brain tissues were negative for MK, PCNA, and p53 protein. We conclude that primary and metastatic tumors of the brain express MK and that the MK expression in brain tumors may depend, in part, on the proliferating potential.

L92 ANSWER 13 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:41728 HCAPLUS
DOCUMENT NUMBER: 140:109558
TITLE: Gene expression in vascular endothelium in normal tissue and in **tumor** angiogenesis and development of anti-angiogenic agents for treatment of cancer
INVENTOR(S): St. Croix, Brad; Kinzler, Kenneth W.; Vogelstein, Bert
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005883	A2	20040115	WO 2003-US16250	20030702

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-393023P P 20020702
US 2003-458964P P 20030401

ED Entered STN: 18 Jan 2004

AB To gain a better understanding of **tumor** angiogenesis, new techniques for isolating endothelial cells (ECs) and evaluating gene expression patterns were developed. When transcripts from ECs derived from normal and malignant colorectal tissues were compared with transcripts from non-endothelial cells, over 170 genes predominantly expressed in the endothelium were identified. Comparison between normal- and **tumor**-derived endothelium revealed many differentially expressed genes, including a large number of genes that were specifically elevated in **tumor**-associated endothelium. Expts. with representative genes from this group demonstrated that most were similarly expressed in the endothelium of primary lung, breast, brain, and pancreatic cancers as well as in **metastatic** lesions of the liver. Theses results demonstrate that **neoplastic** and normal endothelium in **humans** are distinct at the mol. level, and have significant implications for the development of anti-angiogenic agents for treatment of cancer.

L92 ANSWER 14 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:94843 HCAPLUS
DOCUMENT NUMBER: 140:285145
TITLE: Midkine and pleiotrophin in neural development and cancer
AUTHOR(S): Kadomatsu, Kenji; Muramatsu, Takashi
CORPORATE SOURCE: Department of Biochemistry, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, 466-8550, Japan
SOURCE: Cancer Letters (Amsterdam, Netherlands) (2004), 204(2), 127-143
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

ED Entered STN: 05 Feb 2004

AB A review. The midkine (MK) family consists of only two members, namely heparin-binding growth factors MK and pleiotrophin (PTN). During embryogenesis, MK is highly expressed in the mid-gestational period, whereas PTN expression reaches the maximum level around birth. Both proteins are localized in the radial glial processes of the embryonic brain, along which neural stem cells migrate and differentiate. Zebrafish and Xenopus MK can induce neural tissues. In addition, deposits of MK and/or PTN are found in neurodegenerative diseases, such as Alzheimer's disease and multiple system atrophy. Both mols. are induced in reactive astrocytes by ischemic insults. In this context, it is interesting that LDL receptor-related protein is a receptor for MK and PTN, and this receptor has been implicated in the pathogenesis of Alzheimer's disease. MK and PTN share receptors, and show similar biol. activities that include fibrinolytic, anti-apoptotic, mitogenic, transforming, angiogenic, and chemotactic ones. These activities explain how these mols. are involved in carcinogenesis. MK is detected in **human carcinoma** specimens from pre-cancerous stages to advanced stages. Strong expression

of PTN is also detected in several **carcinomas**, although, in general, MK is expressed more intensely and in a wide range of **carcinomas** than PTN. The blood MK level is frequently elevated in advanced **human carcinomas**, decreases after surgical removal of the **tumors**, and is correlated with prognostic factors. Thus, it is a good marker for evaluating the progress of **carcinomas**. Furthermore, antisense oligonucleotides for MK and ribozymes for PTN show anti-**tumor** activity. Therefore, MK and PTN are candidate mol. targets for therapy for **human carcinomas**.

REFERENCE COUNT: 147 THERE ARE 147 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 15 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:626612 HCAPLUS
Correction of: 2003:472599
DOCUMENT NUMBER: 139:129181
Correction of: 139:48232
TITLE: Differentially expressed genes for identification, assessment, prevention, and therapy of colon cancer
INVENTOR(S): Berger, Allison; Guillemette, Tracy L.; Schlegel, Robert; Monahan, John E.; Kamatkar, Shubhangi; Thibodeau, Stephen; Burgart, Lawrence J.
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003050243	A2	20030619	WO 2002-US37431		20021121
WO 2003050243	A3	20040401			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003148410	A1	20030807	US 2002-301822		20021121
PRIORITY APPLN. INFO.:			US 2001-339971P	P	20011210
			US 2002-361978P	P	20020305
			US 2002-381988P	P	20020520

ED Entered STN: 15 Aug 2003
AB The invention relates to newly discovered nucleic mols. and proteins that are up-regulated in colon cancer. The 114 markers were identified by transcriptional profiling with RNA derived from 21 normal colon samples, 4 adenomatous polyps, and 25 colon cancer samples using nylon arrays of 44,200 clones, including 30,000 IMAGE clones, 14,000 clones from cDNA libraries generated at Millennium Pharmaceuticals, Inc., and 200 control genes. Higher than normal levels of expression of any of these markers or combination of these markers correlates with the presence of colon cancer.

Thus, compns., kits, and methods for detecting, characterizing, preventing, and treating **human** colon cancers are provided. The present invention claims a total of 228 sequences, but the Sequence Listing was not made available on publication of the patent application.

L92 ANSWER 16 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1997:772168 HCAPLUS
DOCUMENT NUMBER: 128:70866
TITLE: The serum level of midkine, a heparin-binding growth factor, as a **tumor** marker
AUTHOR(S): Song, Xiao-Jun; Muramatsu, Hisako; Aridome, Kuniaki; Aikou, Takashi; Koide, Norio; Tsuji, Takao; Muramatsu, Takashi
CORPORATE SOURCE: Department of Biochemistry, Nagoya University School of Medicine, Nagoya, 466, Japan
SOURCE: Biomedical Research (1997), 18(5), 375-381
CODEN: BRESD5; ISSN: 0388-6107
PUBLISHER: Biomedical Research Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 11 Dec 1997
AB Midkine (MK) is a heparin-binding growth factor distinct from fibroblast growth factors. Serum levels of MK were determined by enzyme-linked immunoassay using affinity-purified anti-**human** MK antibody. Elevated levels of MK were frequently observed in sera from patients with various **carcinomas** including lung **carcinoma**, bile duct **carcinoma**, colon **carcinoma** and esophageal **carcinoma**. Most patients with lung **carcinoma** showed high MK serum values. In colorectal **carcinoma**, some correlation was observed between high MK value and **tumor** invasion. Surgical removal of **carcinomas** invariably resulted in decreases in the MK level. Determination of serum MK may be useful as an aid in initial screening of certain **carcinomas**, such as lung **carcinoma**.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 17 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1996:439890 HCAPLUS
DOCUMENT NUMBER: 125:137048
TITLE: Enzyme-linked immunoassay for midkine, and its application to evaluation of midkine levels in developing mouse brain and sera from patients with hepatocellular **carcinomas**
AUTHOR(S): Muramatsu, Hisako; Song, Xiao-jun; Koide, Norio; Hada, Hajime; Tsuji, Takao; Kadomatsu, Kenji; Inui, Tatsuya; Kimura, Terutoshi; Sakakibara, Shumpei; Muramatsu, Takashi
CORPORATE SOURCE: Sch. Med., Nagoya Univ., Nagoya, 466, Japan
SOURCE: Journal of Biochemistry (Tokyo) (1996), 119(6), 1171-1175
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 25 Jul 1996
AB Midkine (MK) is a growth factor that promotes neurite outgrowth and survival of neurons, and enhances the plasminogen activator in endothelial cells. A highly sensitive enzyme-linked immunoassay for MK was developed,

involving affinity-purified anti-MK antibodies, their biotinylated form, and avidin-β-galactosidase. The amount of bound avidin-β-galactosidase was determined using a fluorogenic substrate, 4-methylumbelliferyl-β-D-galactoside. This method allowed the detection of **human** and mouse MK in he range of 50 pg-10 ng. Pleiotrophin, which is related to MK in its amino acid sequence, did not show any cross reactivity. Employing this method., the MK levels in the developing mouse brain were determined The MK level was 2 μg/g of wet tissue on the 12th day of gestation, and then steadily decreased during embryogenesis and postnatal development to 30 ng/g two months after birth. The assay method can also be applied to serum samples. Although the MK levels in the sea of normal **human** subjects were low or undetectable, 0.6-8 ng/mL of MK was detected in samples in the majority of cases of hepatocellular **carcinomas**.

L92 ANSWER 18 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:898614 HCAPLUS
DOCUMENT NUMBER: 141:348154
TITLE: **Human** genes showing altered levels of expression in pancreatic **carcinomas** and their diagnostic and therapeutic uses
INVENTOR(S): Rosenthal, Andre; Pilarsky, Christian; Dahl, Edgar; Specht, Thomas; Bruemmendorf, Thomas; Lichtner, Rosemarie; Staub, Eike; Roepcke, Stefan; Li, Xinzhong
PATENT ASSIGNEE(S): Hinzmann, Bernd, Germany; Rosenthal, Andre
SOURCE: Eur. Pat. Appl., 28 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1471075	A2	20041027	EP 2004-90124	20040331
EP 1471075	A3	20050112		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
DE 10315834	A1	20041118	DE 2003-10315834	20030331
PRIORITY APPLN. INFO.:			DE 2003-10315834 A	20030331

ED Entered STN: 28 Oct 2004
AB Genes that show altered levels of expression in pancreatic **carcinoma** are identified for use in the diagnosis of the disease and as possible targets for therapy (no data.). Altered patterns of expression of the gene for protein kinase STK15 is demonstrated.

L92 ANSWER 19 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:16337 HCAPLUS
TITLE: Correlation of elevated plasma levels of two structurally related growth factors, heparin affin regulatory peptide and midkine, in advanced solid **tumor** patients
AUTHOR(S): Soulie, Patrick; Heroult, Melanie; Bernard-Pierrot, Isabelle; Caruelle, Daniele; Oglobine, Jean; Barritault, Denis; Courty, Jose
CORPORATE SOURCE: Laboratoire de Recherche sur la Croissance, la Regeneration et la Reparation Tissulaires, (CRRET), Universite Paris XII-Val de Marne, Creteil, Fr.
SOURCE: Cancer Detection and Prevention (2004), 28(5), 319-324

CODEN: CDPRD4; ISSN: 0361-090X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 09 Jan 2005
AB Heparin affin regulatory peptide (HARP) and midkine (MK) are growth factors, expressed in **carcinomas**, neuroblastomas and gliomas. In this study, the authors measured the levels of HARP and MK in plasma samples from 77 cancer patients. The patients had advanced **tumors** with loco-regional (n = 18) or **metastatic** (n = 49) diseases and 10 patients have their diseases limited to the primary site. HARP and MK plasma concns. were significantly higher in all of these different subgroups of cancer patients ($P < 0.05$ in all cases), when compared to healthy controls (n = 30). Neither HARP nor MK levels were significantly different between patients with loco-regional and **metastatic** **tumors** ($P = 0.203$ and 0.242, resp.). Moreover, a strong correlation between the elevations of the plasma levels of these 2 proteins ($r2 = 0.546$) in these cancer patients was found. Measurements of these secreted angiogenic growth factors may be useful for evaluation of cancer diagnosis.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 20 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:583897 HCAPLUS
DOCUMENT NUMBER: 142:68630
TITLE: Midkine promoter-based conditionally replicative adenovirus for malignant glioma therapy
AUTHOR(S): Kohno, Shohei; Nakagawa, Kou; Hamada, Katsuyuki; Harada, Hironobu; Yamasaki, Kenshi; Hashimoto, Koji; Tagawa, Masatoshi; Nagato, Shigeyuki; Furukawa, Koji; Ohnishi, Takanori
CORPORATE SOURCE: Departments of Neurosurgery, Ehime University School of Medicine, Ehime, 791-0295, Japan
SOURCE: Oncology Reports (2004), 12(1), 73-78
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Jul 2004
AB Little is known concerning promoters or gene therapy specific for malignant glioma. To explore the potential use of midkine promoter in gene therapy for malignant glioma, we constructed a midkine promoter-based conditionally replicating adenovirus (Ad-MK). Midkine was overexpressed in malignant glioma tissues but cyclooxygenase-2 was not. The midkine promoter activity of the 600-bp fragment was 2 orders of magnitude higher in midkine-pos. glioma cells than in midkine-neg. primary normal brain cells. Ad-MK showed strong oncolytic effects in midkine-pos. glioma cells but did not exhibit cytotoxicity in midkine-neg. primary normal brain cells. The cell-killing effect was evident in E3-intact Ad-MK more than in E3-deleted Ad-MK. In an animal experiment, Ad-MK completely eradicated midkine-pos. glioma xenografts. These findings indicate that midkine promoter-based conditionally replicative adenovirus might be a promising new modality of gene therapy for malignant glioma.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 21 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:356613 HCAPLUS

DOCUMENT NUMBER: 138:367673
TITLE: Selection of animal cell lines performing defined post-translational modifications and their use in the manufacture of post-translationally-modified proteins
INVENTOR(S): Opstelten, Dirk Jan Elbertus; Kapteyn, Johan Christiaan; Passier, Petrus Christianus Johannes Josephus; Brus, Ronald Hendrik Peter; Bout, Abraham
PATENT ASSIGNEE(S): Crucell Holland B.V., Neth.
SOURCE: PCT Int. Appl., 175 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003038100	A1	20030508	WO 2002-NL686	20021029
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003050286	A1	20030619	WO 2001-NL792	20011029
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003089468	A1	20031030	WO 2002-NL257	20020419
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1440157	A1	20040728	EP 2002-770322	20021029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013402	A	20041013	BR 2002-13402	20021029

PRIORITY APPLN. INFO.:

WO 2001-NL792	A	20011029
WO 2002-NL257	A	20020419
WO 2002-NL686	W	20021029

ED Entered STN: 09 May 2003
AB Methods of identifying and selecting mammalian cell lines capable of

synthesizing a protein with a preferred pattern of post-translational modifications are described for use in manufacture of the protein. Preferably, the post-translational modifications include glycosylation. Preferably, the protein is erythropoietin (EPO). The biol. activity of EPO manufactured in transgenic host cells depends heavily on its glycosylation pattern. Mammalian cells that have been screened for the patterns of glycosylation are provided. These cells preferably produce neural-type glycosylation patterns on proteins. Patterns of glycosidation of erythropoietin manufactured in PER.C6® cells were analyzed by mass spectrometry of oligosaccharides released by N-glycanase F from gel-purified protein. These cells produced a neural type glycosidation of erythropoietin with extensive fucosylation. They have α1,3- and α1,6-fucosyltransferase activities but no α1,2-fucosyltransferase and accordingly produced Lewis x epitopes, but not Lewis y. This form of erythropoietin was 25-fold less effective at inducing erythropoiesis than that manufactured with serum type glycosidation in CHO cells, but showed a greater neuroprotective effect in cases of cerebral ischemia in a subarachnoid hemorrhage model.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 22 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:577904 HCAPLUS
DOCUMENT NUMBER: 139:129165
TITLE: DNA sequence of antisense oligonucleotide for midkine and its use for repression the expression of midkine in **human** cell line
INVENTOR(S): Takei, Yoshifumi; Kadomatsu, Kenji; Muramatsu, Takashi
PATENT ASSIGNEE(S): Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003210170	A2	20030729	JP 2002-47135	20020118

PRIORITY APPLN. INFO.: JP 2002-47135 20020118
ED Entered STN: 29 Jul 2003
AB The invention provides a DNA sequence of antisense oligonucleotide for midkine. Compared to control, the expression of midkine antisense oligonucleotide repressed expression of midkine by 27 % in **human** cell line SW620. The midkine antisense oligonucleotide provided in this invention can be used as anticancer agents.

L92 ANSWER 23 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:208714 HCAPLUS
DOCUMENT NUMBER: 139:4559
TITLE: Immunohistochemical and quantitative competitive PCR analyses of midkine and pleiotrophin expression in cervical cancer
AUTHOR(S): Moon, Hye-Sung; Park, Won I.; Sung, Sun Hee; Choi, Eun-Ah; Chung, Hye-Won; Woo, Bock Hi
CORPORATE SOURCE: Department of Obstetrics & Gynecology, Ewha Womans University and Medical Research Center, Seoul, S. Korea
SOURCE: Gynecologic Oncology (2003), 88(3), 289-297

CODEN: GYNOA3; ISSN: 0090-8258
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 18 Mar 2003
AB The aim of this study was to determine midkine (MK) and pleiotrophin (PTN) expression in cervical cancer. Prospective study in tertiary teaching hospital. Normal and cancerous cervical tissues were obtained from healthy women (n = 19) and from patients with cervical cancer (n = 42). The expressions of MK and PTN mRNA and protein were examined by quant. competitive PCR and by immunohistochem. MK and PTN mRNA and protein expressions were examined with respect to **tumor** stage and size. The expressions of midkine and pleiotrophin mRNA in cervical cancer were higher than those in the normal cervix (MK, 175.59 ± 63.3 vs 1.00 ± 0.18 fmol, resp.; PTN, 3.18 ± 1.25 vs. 0.86 ± 0.12 fmol, resp., P < 0.05), and their expressions were not correlated with cervical cancer stage or size of the **tumor**. The expressions of MK and PTN protein in cancerous tissue were higher than those in the normal cervix (P < 0.05). Moreover, the protein expression of MK, but not of PTN, correlated with **tumor** stage and size. The expressions of MK and PTN were not correlated with vascular d. These results suggest that increased midkine mRNA and protein expressions are associated with the carcinogenesis of cervical cancer.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 24 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:923208 HCAPLUS
DOCUMENT NUMBER: 140:314324
TITLE: Utilization of the promoter region of the midkine gene as a tool to drive therapeutic genes in a **tumor** specific manner
AUTHOR(S): Sakiyama, Shigeru; Yu, Ling; Tomizawa, Minoru; Shimada, Hideaki; Kadomatsu, Kenji; Muramatsu, Takashi; Ikematsu, Shinya; Nakagawara, Akira; Tagawa, Masatoshi
CORPORATE SOURCE: Chiba Cancer Center Research Institute, Chuoh-ku, Chiba, 260-8717, Japan
SOURCE: Advances in Enzyme Regulation (2003), 43, 57-66
CODEN: AEZRA2; ISSN: 0065-2571
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 26 Nov 2003
AB A system for measuring midkine (MK) in **human** serum using enzyme-linked immunoassay was described. The system confirmed the usefulness of measuring MK level in sera of patients of neuroblastoma and esophageal cancer patients as a prognostic marker. The investigations on the 2.3 kb MK promoter with a reporter assay for its transactivation of the fused luciferase gene in various **tumor** cell lines was investigated showed that the minimal promoter activity resides in the region of 0.3-kb adjacent to the transcription initiation site. Further anal. revealed that 0.6-kb fragment spanning further upstream of Mkp-0.3kb mediated the preferential transcription in immortalized cells. These findings suggest that the **tumor**-specific expression of therapeutic gene(s) can be achieved by the use of cis-acting MK promoter.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 25 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:964539 HCAPLUS
DOCUMENT NUMBER: 138:34222
TITLE: Differentially expressed **human** genes and their encoded proteins useful for identification, assessment, prevention, and therapy of cervical cancer
INVENTOR(S): Schlegel, Robert; Chen, Yan; Zhao, Xumei; Monahan, John E.; Kamatkar, Shubhangi; Gannavarapu, Manjula; Glatt, Karen; Hoersch, Sebastian
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 386 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002101075	A2	20021219	WO 2002-US18638		20020612
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003087270	A1	20030508	US 2002-171311		20020612
PRIORITY APPLN. INFO.:			US 2001-298155P	P	20010613
			US 2001-298159P	P	20010613
			US 2001-335936P	P	20011114

ED Entered STN: 20 Dec 2002
AB The invention relates to 119 newly discovered nucleic acid mols. and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia in **human** patients. Cervical **tumor** -specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical **tumors**, 5 CIN III, 5 CIN I, and 12 normal cervical tissues. The top up-regulated clones in **tumors** or DIN III cervical tissues, as determined by proprietary statistical anal. methods, were selected, and full-length clones obtained by contiguous assembly of EST sequences. Compns., kits, and methods for detecting, characterizing, preventing, and treating **human** cervical cancers are provided.

L92 ANSWER 26 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:276203 HCAPLUS
DOCUMENT NUMBER: 136:290017
TITLE: Gene expression profiles in hepatocellular carcinoma and metastatic liver cancer
INVENTOR(S): Horne, Darci; Alvares, Christopher; Peres da Silva, Supriya; Vockley, Joseph G.
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 298 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002029103	A2	20020411	WO 2001-US30589		20011002
WO 2002029103	A3	20030904			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2002142981	A1	20021003	US 2001-880107		20010614
AU 2002011313	A5	20020415	AU 2002-11313		20011002
PRIORITY APPLN. INFO.:			US 2000-237054P	P	20001002
			US 2000-211379P	P	20000614
			WO 2001-US30589	W	20011002

ED Entered STN: 12 Apr 2002

AB The present invention identifies the global changes in gene expression associated with liver cancer by examining gene expression in tissue from normal liver, metastatic malignant liver and hepatocellular carcinoma (HCC). Gene signatures were obtained by hybridizing cDNA from liver samples mRNA onto the Affymetrix HuGeneFl array and the Human Hu35k set of arrays. There are 8479 genes and ESTs in the pos. Gene Signature for the HCC tumors, and a total of 23,233 genes and ESTs are included in the neg. Gene Signature of the HCC samples (e.g., all the genes that have been completely turned off during tumorigenesis, as well as those genes that are not usually expressed in liver tissue). A differential comparison of the genes and ESTs expressed in the normals and the two different types of liver tumors identifies a subset of the genes included in the pos. Gene Signatures that are uniquely expressed in each sample set. A number of the tumor-expressing genes are closely examined to determine if their expression patterns correlate with previous reports published in the literature, and to define a logical relationship between the gene and hepatocarcinogenesis. The present invention also identifies expression profiles which serve as useful diagnostic markers as well as markers that can be used to monitor disease states, disease progression, drug toxicity, drug efficacy and drug metabolism

L92 ANSWER 27 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2002:341307 HCAPLUS
DOCUMENT NUMBER:	136:368453
TITLE:	Preparation of monoclonal antibody specific to **truncated midkine** and the use of antibody for detection of **tumor** cells
INVENTOR(S):	Mitsumoto, Tomohiro; Shinozawa, Takao
PATENT ASSIGNEE(S):	Denka Seiken Co., Ltd., Japan
SOURCE:	Jpn. Kokai Tokkyo Koho, 11 pp. CODEN: JKXXAF
DOCUMENT TYPE:	Patent
LANGUAGE:	Japanese
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

JP 2002125666	A2	20020508	JP 2000-330325	20001030
US 2004219614	A1	20041104	US 2003-427961	20030502
PRIORITY APPLN. INFO.:			JP 2000-330325 A	20001030

ED Entered STN: 08 May 2002

AB This invention provides a process for preparation of monoclonal antibody specific to truncated midkine (tMK). The antibody can be used for detection of **human tumor** cells where the tMK highly expressed.

L92 ANSWER 28 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:419546 HCAPLUS
DOCUMENT NUMBER: 138:32914
TITLE: A promoter region of midkine gene can activate transcription of an exogenous suicide gene in **human** pancreatic cancer
AUTHOR(S): Yoshida, Yu; Tomizawa, Minoru; Bahar, Rumana; Miyauchi, Motohiro; Yamaguchi, Taketo; Saisho, Hiromitsu; Kadomatsu, Kenji; Muramatsu, Takashi; Matsubara, Shuichiro; Sakiyama, Shigeru; Tagawa, Masatoshi
CORPORATE SOURCE: Division of Pathology, Chiba, 260-8717, Japan
SOURCE: Anticancer Research (2002), 22(1A), 117-120
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 04 Jun 2002

AB We examined a possible application of regulatory regions of the midkine (MK) gene for suicide gene therapy of pancreatic cancer. The expression of MK has been demonstrated in **human** pancreatic cancer tissues but scarcely in normal adult tissues. Northern blot anal. confirmed that **human** pancreatic cancer cell lines expressed the MK gene. A 609-bp genomic fragment in the 5'-regulatory region of the MK gene, when transfected into **human** pancreatic cancer cells, activated the transcription of a fused reporter gene to an extent greater than the SV40 promoter. In contrast, the 609-bp fragment-mediated promoter activity tested in fibroblast cells was significantly weak. **Human** pancreatic cancer cells (AsPC-1) that were transduced with the herpes simplex virus-thymidine kinase gene linked with the 609-bp promoter markedly increased their sensitivity to a prodrug, ganciclovir, compared with untransduced cells. The present study suggests that preferential cytotoxic effects for pancreatic **tumors** can be achieved by using the MK promoter.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 29 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:923849 HCAPLUS
DOCUMENT NUMBER: 136:32174
TITLE: Pleiotrophin growth factor receptor for the treatment of proliferative, vascular and neurological disorders
INVENTOR(S): Wellstein, Anton
PATENT ASSIGNEE(S): Georgetown University Medical Center, USA
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096394	A2	20011220	WO 2001-US18938	20010614
WO 2001096394	A3	20030306		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2412650	AA	20011220	CA 2001-2412650	20010614
US 2002034768	A1	20020321	US 2001-880097	20010614
EP 1305337	A2	20030502	EP 2001-944466	20010614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			US 2000-211491P P	20000614
			WO 2001-US18938 W	20010614

ED Entered STN: 21 Dec 2001

AB This invention relates to the discovery that pleiotrophin binds to and activates a pleiotrophin-receptor which is responsible for the events associated with pleiotrophin activity including **tumorigenesis**, cell proliferation, and cell invasion. By interfering with that association, the cascade of events associated with pleiotrophin activity can be prevented or reversed. Further, by evaluating the effect of different compds. and conditions on the interaction, new drugs and treatments can be identified for use in preventing certain cancers and growth and developmental disorders. Specifically claimed are isolated polypeptide complexes comprising a pleiotrophin protein and a pleiotrophin-receptor protein; addnl. claimed are recombinant polypeptides comprising one or more, but not all regions of a full-length pleiotrophin receptor protein and recombinant polypeptides comprising regions of a pleiotrophin. Nucleic acids which encode the polypeptides of the invention and compns. comprising the polypeptides of the invention are also claimed, as are antibodies reactive against a pleiotrophin protein. Kits comprising a pleiotrophin-binding region of a pleiotrophin-receptor protein and a pleiotrophin-receptor binding region of a pleiotrophin protein, for screening a substance for the ability to block interaction between pleiotrophin and pleiotrophin receptor are also claimed.

L92 ANSWER 30 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:8986 HCAPLUS

DOCUMENT NUMBER: 136:272791

TITLE: Midkine and cyclooxygenase-2 promoters are promising for adenoviral vector gene delivery of pancreatic **carcinoma**

AUTHOR(S): Wesseling, John G.; Yamamoto, Masato; Adachi, Yasuo; Bosma, Piter J.; Van Wijland, Michel; Blackwell, Jerry L.; Li, Hui; Reynolds, Paul N.; Dmitriev, Igor; Vickers, Salwyn M.; Huibregtse, Kees; Curiel, David T.

CORPORATE SOURCE: Department of Experimental Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, 1105 AZ, Neth.

SOURCE: Cancer Gene Therapy (2001), 8(12), 990-996
CODEN: CGTHEG; ISSN: 0929-1903

PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 04 Jan 2002
AB Midkine (MK), a heparin binding growth factor, and cyclooxygenase-2 (COX-2), a key enzyme in the conversion of arachidonic acid to prostaglandin, are both up-regulated at the mRNA or protein level in many **human** malignant **tumors**. Here, we investigated the **tumor** specificity of both MK and COX-2 promoters in **human** pancreatic cancer, with the aim to improve the selectivity of therapeutic gene expression. We constructed recombinant adenoviral (Ad) vectors containing either the luciferase (Luc) reporter gene under the control of the COX-2 or MK promoter or the herpes simplex virus thymidine kinase (HSV Tk) gene under the control of the COX-2 promoter and compared the expression with the cytomegalovirus (CMV) promoter. AdMKLuc achieved moderate to relatively high activity upon infection to both primary and established pancreatic **carcinoma** cells. Of the two COX-2 promoter regions (COX-2M and COX-2L), both revealed a high activity in primary pancreatic **carcinoma** cells, whereas in the established pancreatic **carcinoma** cell lines, COX-2L has an approx. equal high activity compared to CMV. In addition, both AdCOX-2M Tk and AdCOX-2L Tk induced marked cell death in response to ganciclovir (GCV) in three of four established pancreatic **carcinoma** cell lines. From these results, and because it has been reported that AdMKTk and AdCOX-2L Tk in combination with GCV did not reveal significant liver toxicity, we conclude that the MK as well as the COX-2 promoters are promising **tumor**-specific promoters for Ad vector-based gene therapy of pancreatic cancer.

L92 ANSWER 31 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:686505 HCAPLUS
DOCUMENT NUMBER: 133:265646
TITLE: Antibody and immunoassay for detecting midkine in clinical sample
INVENTOR(S): Yano, Akira
PATENT ASSIGNEE(S): Meiji Milk Products, Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000266750	A2	20000929	JP 1999-70734	19990316
PRIORITY APPLN. INFO.:			JP 1999-70734	19990316

ED Entered STN: 29 Sep 2000
AB Provided is a highly sensitive method for detecting **human** midkine in clin. samples using anti-midkine antibody. The immunoassay method is an ELISA performed in a reaction buffer with ionic strength 0.3-1.5, adjusted with salts, e.g. potassium chloride. The method is useful for diagnosis of midkine-related diseases, e.g. tissue repair and nerve extension, cancer development, etc.

L92 ANSWER 32 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:334370 HCAPLUS
DOCUMENT NUMBER: 125:31093
TITLE: The angiogenic factor midkine is expressed in bladder

cancer, and overexpression correlates with a poor outcome in patients with invasive cancers
AUTHOR(S): O'Brien, Tim; Cranston, David; Fuggle, Susan; Bicknell, Roy; Harris, Adrian L.
CORPORATE SOURCE: Molecular Angiogenesis Group, Imperial Cancer Res. Fund., Inst. Molecular Med., Nuffield Dep. Surgery, Univ. Oxford, Oxford, OX3 9DU, UK
SOURCE: Cancer Research (1996), 56(11), 2515-2518
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 08 Jun 1996
AB Midkine (MK) is a member of a family of heparin-binding growth factors, which are reported to be angiogenic. We have investigated by RNase protection anal. the expression of MK in 47 primary bladder **tumors** and 7 normal bladder samples. MK mRNA transcripts were detectable in 46 (98%) of 47 of the **tumors** and in 5(70%) of 7 of the normal bladder samples. However, median MK expression was 4-fold higher in **tumors** than in the normal bladder ($P < 0.004$). In eight **tumors** (17%), MK expression was elevated more than 10-fold compared with the median value of the normal bladder specimens. There was no statistically significant difference in expression between superficial and invasive **tumors** ($P < 0.50$). Seven (32%) of 22 patients with invasive cancers are alive at 1 yr with no evidence of recurrence; in 5 (70%) of these patients, MK expression in the **tumor** was within the normal range at the time of presentation. By contrast, in only 2 (13%) of 15 patients who died or whose **tumors** recurred or progressed was MK expression in the normal range ($P < 0.01$). Overall, median MK expression in invasive **tumors** that caused death, progressed, or recurred within 12 mo was 3-fold higher than that found in the **tumors** of those patients who were clear of disease as 12 mo ($P < 0.04$). Thus, overexpression of MK is associated with the development of bladder cancer and in invasive cancers predicts a poor clin. outcome in the short term.

L92 ANSWER 33 OF 40 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 7
ACCESSION NUMBER: 2002348158 EMBASE
TITLE: Midkine and pleiotrophin: Two related proteins involved in development, survival, inflammation and tumorigenesis.
AUTHOR: Muramatsu T.
CORPORATE SOURCE: T. Muramatsu, Department of Biochemistry, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. tmurama@med.nagoya-u.ac.jp
SOURCE: Journal of Biochemistry, (1 Sep 2002) 132/3 (359-371).
Refs: 180
ISSN: 0021-924X CODEN: JOBIAO
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Midkine (MK) and pleiotrophin (PTN) are low molecular weight proteins with closely related structures. They are mainly composed of two domains held by disulfide bridges, and there are three antiparallel β-sheets in each domain. MK and PTN promote the growth, survival, and migration of various cells, and play roles in neurogenesis and epithelial mesenchymal interactions during organogenesis. A chondroitin sulfate proteoglycan,

protein-tyrosine phosphatase ζ (PTPζ), is a receptor for MK and PTN. The downstream signaling system includes ERK and PI3 kinase. MK binds to the chondroitin sulfate portion of PTPζ with high affinity. Among the various chondroitin sulfate structures, the E unit, which has 4,6-disulfated N-acetylgalactosamine, provides the strongest binding site. The expression of MK and PTN is increased in various human tumors, making them promising as tumor markers and as targets for tumor therapy. MK and PTN expression also increases upon ischemic injury. MK enhances the migration of inflammatory cells, and is involved in neointima formation and renal injury following ischemia. MK is also interesting from the viewpoints of the treatment of neurodegenerative diseases, increasing the efficiency of in vitro development, and the prevention of HIV infection.

L92 ANSWER 34 OF 40 EMBASE
on STN
ACCESSION NUMBER: 2001068434 EMBASE
TITLE: Production and characterization of a bacterial single-chain Fv fragment specific to human truncated midkine.
AUTHOR: Dansithong W.; Paul S.; Mitsumoto T.; Saruhashi S.; Shinozawa T.
CORPORATE SOURCE: T. Shinozawa, Dept. of Biological/Chemical Eng., Faculty of Engineering, Gunma University, Kiryu, Gunma 376-8515, Japan. shinozawa@bce.gunma-u.ac.jp
SOURCE: Cancer Letters, (26 Mar 2001) 164/2 (169-176).
Refs: 24
ISSN: 0304-3835 CODEN: CALEDQ
PUBLISHER IDENT.: S 0304-3835(01)00376-7
COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The production (and characterization) of a monoclonal antibody against human truncated midkine (tMK), and the detection of tMK in G401 cells, a Wilms' tumor cell line, as well as in Wilms' tumor patient specimens, have been reported (Paul et al., Cancer Lett. 163 (2001) 245-251). Here we report the molecular cloning and expression of this monoclonal antibody as a single-chain Fv fragment (scFv) in Escherichia coli. The scFv protein, purified by immobilized metal affinity chromatography, showed a specific affinity to recombinant tMK and native tMK in G401 cells as detected by enzyme-linked immunosorbent assay and immunofluorescence microscopy, respectively. The binding of this protein to recombinant tMK was competitive with the parental monoclonal antibody. These results suggest that this scFv can also be used for Wilms' tumor detection. .COPYRGT. 2001 Elsevier Science Ireland Ltd.

L92 ANSWER 35 OF 40 EMBASE
on STN
ACCESSION NUMBER: 1999357909 EMBASE
TITLE: Immunohistochemical analysis of Midkine expression in human prostate carcinoma.
AUTHOR: Konishi N.; Nakamura M.; Nakaoka S.; Hiasa Y.; Cho M.; Uemura H.; Hirao Y.; Muramatsu T.; Kadomatsu K.
CORPORATE SOURCE: Dr. N. Konishi, Second Department of Pathology, Nara Medical University, Kashihara, Nara 634-8521, Japan.

nkonishi@naramed-u.ac.jp
SOURCE: Oncology, (1999) 57/3 (253-257).
Refs: 23
ISSN: 0030-2414 CODEN: ONCOBS
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Midkine (MK) is a growth/differentiation factor frequently expressed at high levels in some types of human malignancies. To investigate whether MK is a useful marker in prostate carcinogenesis, immunohistochemical analysis was performed on samples of both latent and clinical prostate cancers of various stages, as well as on specimens of normal gland and prostatic intraepithelial neoplasia (PIN). Of the 80 clinical cancers examined, 69 specimens (86.3%) were immunoreactive for MK, with metastatic lesions generally showing higher expression than the corresponding primaries; normal prostate tissues were negative or showed only weak staining. Midkine was also detected in 12 of 15 latent cancers (80%) and in 12 of 16 cases of PIN (75%). In sections of whole prostate, MK showed variable expression through tumorous sections, probably in reflection of heterogeneous cell populations. The results demonstrate the possible value of MK as a marker for early and latent disease, as well as for more advanced clinical stages of prostate cancer.

L92 ANSWER 36 OF 40 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:445560 BIOSIS
DOCUMENT NUMBER: PREV200400440432
TITLE: Correlation between **midkine** protein overexpression in hepatocellular **carcinoma** with the presence of **tumor** cells in the **blood** circulation.
AUTHOR(S): Yin Zhengfeng [Reprint Author]; Kang Xiaoyan; Luo Xiangji; et al.
CORPORATE SOURCE: Eastern Hepatobilliary Surg HospDept Mol Oncol, Second Mil Med Univ, Shanghai, China
SOURCE: Zhongguo Zhongliu Linchuang, (April 2004) Vol. 31, No. 7, pp. 361-364. print.
ISSN: 1000-8179.
DOCUMENT TYPE: Article
LANGUAGE: Chinese
ENTRY DATE: Entered STN: 17 Nov 2004
Last Updated on STN: 17 Nov 2004
ED Entered STN: 17 Nov 2004
Last Updated on STN: 17 Nov 2004
AB Objective: To investigate the **midkine** protein expression in human hepatocellular **carcinoma** (HCC) and its relation to **cancer** cell blood dissemination. Methods: Circulating **tumor** cells were detected in preoperative blood samples using reverse transciption polymerase chain reaction (RTPCR) for alpha-fetoprotein (AFP) mRNA. **Midkine** expression was immunohistochemically examined on surgically resected HCC tissues. Results: Fortyone HCC patients with **serum** AFP positive were studied. Positive AFP mRNA expression was showed in 18 preoperative blood samples (43.9%) and **midkine** overexpression was detected in 29 excised **tumors** (70.7%). Among the 29 patients, 18 (62.1%)

showed AFP mRNA positive in their pre-operative blood samples. In contrast, the positive AFP mRNA expression was only observed in 3 out of 12 patients (25.0%) without aberrant **midkine** expression. Statistical analysis showed that abnormal **midkine** expression in the **tumors** was a varial significantly associated with the presence of **tumor** cells in the blood circulation (P0.05). Conclusion: In human hepatocellular **carcinoma, midkine** overexpression is correlated with a haematogenuous spread of the primary **tumor** cells, may be a marker of **tumor metastatic** potential.

L92 ANSWER 37 OF 40 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:195324 BIOSIS
DOCUMENT NUMBER: PREV200200195324
TITLE: **Immunoassay** for measuring the heparin-binding growth factors HARP and MK in biological fluids.
AUTHOR(S): Soulie, Patrick; Heroult, Melanie; Bernard, Isabelle; Kerros, Marie-Emmanuelle; Milhiet, Pierre Emmanuel; Delbe, Jean; Barritault, Denis; Caruelle, Daniele; Courty, Jose [Reprint author]
CORPORATE SOURCE: Laboratoire de Recherche sur la Croissance Cellulaire la Reparation et la Regeneration Tissulaires (CRRET), UPRES-A CNRS 7053, Universite Paris XII, Val de Marne avenue du General de Gaulle, 94010, Creteil, France courty@univ-paris12.fr
SOURCE: Journal of Immunoassay and Immunochemistry, (February, 2002) Vol. 23, No. 1, pp. 33-48. print. ISSN: 1532-1819.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2002 Last Updated on STN: 13 Mar 2002
ED Entered STN: 13 Mar 2002 Last Updated on STN: 13 Mar 2002
AB Heparin-affin regulatory peptide (HARP) and **Midkine** (MK) belong to a family of growth/differentiation factors that have a high affinity for heparin. The involvement of these molecules in various proliferative diseases prompted us to develop an assay for measuring the concentrations of these factors in biological fluids and culture media. This report describes an immunoassay that uses only commercially available materials, based on the high affinity of certain molecules for heparin. It consists of adsorbing heparin-BSA covalent complexes to microtiter plate wells and to quantify the heparin bound HARP or MK by using appropriate antibody. The method is specific and measures concentrations ranging from 40-1200 pg/mL HARP and from 25-1200 pg/mL MK and various parameters are investigated. The within-assay coefficient of variation was less than 5% for both assays. The method was checked by measuring the concentrations of these growth factors in the **sera** of healthy humans and in patients with **cancer**. As previously reported, we confirmed that the **serum** concentrations of MK are higher in patients with **tumours** (n = 139) than in controls (n = 19). The synthesis of HARP and MK by various cells in culture was also analysed.

L92 ANSWER 38 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-468816 [44] WPIX

DOC. NO. CPI: C2004-175716
TITLE: New polypeptide, useful for **diagnosing** or treating e.g. reproductive, cell proliferative disorders, inflammatory, cardiovascular, neurological or metabolic disorders or viral, bacterial, fungal or parasitic infection.
DERWENT CLASS: B04 D16
INVENTOR(S): FAGAN, R J; LEVITA, C; MICHALOVICH, D; YORKE, M
PATENT ASSIGNEE(S): (ARES-N) ARES TRADING SA
COUNTRY COUNT: 107
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004052928	A2	20040624	(200444)*	EN	98
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003295100	A1	20040630	(200472)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004052928	A2	WO 2003-GB5374	20031210
AU 2003295100	A1	AU 2003-295100	20031210

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003295100	A1 Based on	WO 2004052928

PRIORITY APPLN. INFO: GB 2002-28776 20021210
AB WO2004052928 A UPAB: 20040712
NOVELTY - A new polypeptide does not comprise an 8-amino acid sequence but comprises:
(1) a 74-amino acid sequence;
(2) a fragment of (a) comprising a fragment of the 21-amino acid sequence, where the polypeptide has the activity of the 156- or 134-amino acid sequence or has an antigenic determinant that is specific to the 74-amino acid sequence; or
(3) an equivalent of (a) or (b).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a purified mRNA or cDNA nucleic acid molecule or its complement encoding the polypeptide;
(2) a vector comprising a nucleic acid molecule;
(3) a host cell transformed with the vector;
(4) a ligand which binds specifically to the polypeptide;
(5) a compound that either increases or decreases the level of expression or activity of the polypeptide;
(6) **diagnosing** a disease in a patient;
(7) a pharmaceutical composition comprising the polypeptide, nucleic acid molecule, vector, host cell, ligand or compound;

(8) treating a disease in a patient;
(9) monitoring the therapeutic treatment of disease in a patient;
(10) identifying a compound **diagnosing** or treating a disease;
(11) a kit for **diagnosing** disease;
(12) a transgenic or knockout non-human animal that has been transformed to express higher, lower or absent levels of the polypeptide; and
(13) screening for a compound for treating disease.
ACTIVITY - Cytostatic; Virucide; Neuroprotective; Antiinflammatory; Antipsoriatic; Cardiant; Antidiabetic; Antibacterial; Vulnerary; Osteopathic; Anorectic; Gastrointestinal; Fungicide; Antiparasitic; Hypotensive; Antiarteriosclerotic; Respiratory-Gen; Analgesic; Nephrotropic.
No biological data given.
MECHANISM OF ACTION - Gene therapy; Vaccine.
USE - The polypeptide is useful as a growth factor or as a modulator of growth factor activity for preparing a composition for **diagnosing** or treating reproductive disorders, cell proliferative disorders, including **neoplasm**, melanoma, lung, colorectal, breast, pancreas, head and neck and other solid **tumors**; stomach **cancer**, colon **cancer**, pancreatic **cancer**, lung **cancer**, thoracic **cancer** or liver **cancer**; myeloproliferative disorders, such as leukemia, non-Hodgkin lymphoma, leukopenia, thrombocytopenia, angiogenesis disorder, Kaposis' sarcoma; autoimmune/inflammatory disorders, including allergy, inflammatory bowel disease, pancreatitis, arthritis, psoriasis, psoriasis vulgaris, respiratory tract inflammation, asthma, and organ transplant rejection; cardiovascular disorders, including hypertension, edema, angina, atherosclerosis, thrombosis, sepsis, shock, reperfusion injury, and ischemia, particularly ischemic heart disease; neurological disorders including central nervous system disease, Alzheimer's disease, brain injury, Parkinson's disease, amyotrophic lateral sclerosis, and pain; developmental disorders; metabolic disorders including diabetes mellitus, osteoporosis, and obesity, AIDS, renal disease, particularly idiopathic nephrotic syndrome; disorders related to fibrinolysis; neutrophilic functional disorders (e.g. lazy-leukocyte (chemotaxis-deficient leukocyte) syndrome); inflammatory diseases; wound healing disorders; lung injury; infections including viral infection, bacterial infection, fungal infection and parasitic infection or other pathological conditions (claimed).
Dwg.0/13
ABEX UPTX: 20040712
EXAMPLE - No relevant examples given.

L92 ANSWER 39 OF 40 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-248087 [24] WPIX
CROSS REFERENCE: 2004-143953 [14]
DOC. NO. NON-CPI: N2003-197120
DOC. NO. CPI: C2003-063947
TITLE: Specific nucleic acids or proteins as markers of hepatocellular **carcinoma**, useful for **diagnosis**, treatment and drug screening.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): DEBUSCHEWITZ, S; JOBST, J; KAISER, S
PATENT ASSIGNEE(S): (DEBU-I) DEBUSCHEWITZ S; (JOBS-I) JOBST J; (KAIS-I) KAISER S
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003010336	A2	20030206	(200324)*	GE	98
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
DE 10136273	A1	20030213	(200324)		
AU 2002333275	A1	20030217	(200452)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003010336	A2	WO 2002-EP8305	20020725
DE 10136273	A1	DE 2001-10136273	20010725
AU 2002333275	A1	AU 2002-333275	20020725

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002333275	A1 Based on	WO 2003010336

PRIORITY APPLN. INFO: DE 2001-10136273 20010725

AB WO2003010336 A UPAB: 20040813

NOVELTY - Use of specific nucleic acids (I), or polypeptides (II) encoded by them, as markers for hepatocellular **carcinoma** (HCC), is new.

DETAILED DESCRIPTION - Use of specific nucleic acids (I), or polypeptides (II) encoded by them, as markers for hepatocellular **carcinoma** (HCC). (I) is:

(i) any of about 1100 genes (tabulated);

(ii) an equivalent of (i) within the degeneracy of the genetic code;

(iii) a fragment of (i) or (ii) containing at least 20, best 100, nucleotides;

(iv) a sequence that hybridizes to (i)-(iii) under stringent conditions; or

(v) the complement of (i)-(iv).

INDEPENDENT CLAIMS are also included for the following:

(1) **diagnosis** of HCC using at least one (I) as probe;

(2) treatment of HCC by modulating the amount of at least one (I);

(3) HCC-specific cluster containing at least 60 (I); and

(4) expression profile associated with HCC containing at least 60 (I).

ACTIVITY - Cytostatic; Hepatotropic; Virucide; Antiinflammatory. No biological data is given.

MECHANISM OF ACTION - Modulation of gene expression/protein activity.

USE - (I) and (II) are useful for **diagnosis** and treatment of HCC, also for identifying new agents for treatment. They can also be used for differential **diagnosis** between HCC caused by hepatitis B or hepatitis C viruses, and HCC and cholangiocellular **carcinoma** (claimed), or, not claimed, between benign and malignant liver **tumors** (adenoma/**carcinoma**); between **metastases** to liver of bowel **cancer** and HCC; and between alcohol-associated and other forms of HCC. They may also be used to stage **cancers**.

Dwg.0/7

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ACCESSION NUMBER: 2000-400190 [34] WPIX
DOC. NO. NON-CPI: N2000-299756
DOC. NO. CPI: C2000-120933
TITLE: **Diagnosing** and/or treating a neurofibromatosis type I disorders by quantifying **midkine** expression levels in the skin and serum.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): KURTZ, A C; MARTUZA, R L; MASHOUR, G A
PATENT ASSIGNEE(S): (GEOU) UNIV GEORGETOWN
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000031541	A2	20000602	(200034)*	EN	32
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000031541	A2	WO 1999-US27292	19991118

PRIORITY APPLN. INFO: US 1998-109404P 19981120
AB WO 200031541 A UPAB: 20000718
NOVELTY - A method (I) for **diagnosing** and/or treating a neurofibromatosis type I disorder in an individual, comprising quantifying the level of **midkine** protein or **midkine** mRNA in a sample from the patient, and comparing that value to the **midkine** protein/mRNA levels detected in healthy individuals, is new.

DETAILED DESCRIPTION - A method (I) for **diagnosing** and/or treating a neurofibromatosis type I disorder in an individual, comprising:

(1) obtaining a skin sample from the individual; and

(2) detecting the presence of **midkine** proteins and/or the mRNA sequence encoding the **midkine** protein in the skin sample (the presence of a detectable amount of **midkine** protein and/or mRNA in the sample indicates the likelihood of a neurofibromatosis type I disorder.

An INDEPENDENT CLAIM is also included for a method (II) for culturing tissue cells, comprising:

(a) adding a **midkine** protein to a culture medium containing the tissue cells; and

(b) culturing the tissue cells in solution.

USE - (I) may be used for the **diagnosis** and treatment of neurofibromatosis type I disorders in patients (claimed).

Dwg.0/3

ABEX UPTX: 20000718
EXAMPLE - Neurofibromin is expressed in Schwann cells (see Nakamura T et al., Specific expression of the neurofibromatosis type 1 (NF1) gene in the hamster Schwann cell, Am. J Pathol 144(3):549-555 (1994)) and its loss in these cells results in the up regulation of midkine (MK)-1. Because neurofibromin is also expressed in keratinocytes and melanocytes (see Malhotra et al., Localization of pleiotrophin and midkine in the postnatal developing cerebellum, Neurosci. Lett. 178(2):216-220 (1994)), and because

the symptoms of NF1 are predominantly cutaneous, the levels of MK-1 were assayed to determine whether MK is abnormally up regulated in the skin of NF-1 patients. In situ hybridization (ISH) revealed dramatic expression of MK transcripts in the keratinocytes of NF-1 patients. MK mRNA was detected in the skin of NF-1 patients in all layers of epidermis overlying neurofibromas, and was also found in cells of dermal neurofibromas. Importantly, skin over a solitary neurofibroma from a non-NF-1 subject demonstrated little or no MK expression, suggesting that expression was particular to NF-1 patients. Skin without phenotypic abnormalities from an NF-1 patient was also found to be positive for MK, while normal skin from healthy subjects was negative for MK expression by ISH and Northern analysis. No signal was detected using a MK sense riboprobe. This data showed that the induction of MK expression in neurofibromin-deficient keratinocytes is linked to the NF-1 mutation itself, and not simply to the presence of an underlying neurofibroma.

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